HEPATAMINE - isoleucine, leucine, lysine acetate, methionine, phenylalanine, threonine, tryptophan, valine, alanine, arginine, histidine, proline, serine, glycine and cysteine hydrochloride injection

B. Braun Medical Inc.

Protect from light until use.

DESCRIPTION

HepatAmine (8% Amino Acid Injection) is a sterile, nonpyrogenic, hypertonic solution containing crystalline amino acids. A 500 mL unit provides a total of 40 g of amino acids and 6 g of nitrogen (38 g of protein equivalent).

Each 100 mL contains:

Essential Amino Acids

Isoleucine USP.....0.90 g
Leucine USP.....1.10 g
Lysine.....0.61 g
(added as Lysine Acetate USP.....0.86 g)
Methionine USP.....0.10 g
Phenylalanine USP.....0.10 g
Threonine USP.....0.45 g
Tryptophan USP.....0.066 g
Valine USP.....0.84 g

Nonessential Amino Acids

Alanine USP.....0.77 g
Arginine USP.....0.60 g
Histidine USP.....0.24 g
Proline USP.....0.80 g
Serine USP.....0.50 g
Glycine USP.....0.90 g
Cysteine.....<0.014 g
(as Cysteine HCl•H_2O USP.....<0.020 g)
Phosphoric Acid NF.....0.115 g
Sodium Bisulfite (as an antioxidant).....<0.1 g
Water for Injection USP.....qs
pH adjusted with Glacial Acetic Acid USP
pH: 6.5 (6.0–6.8)
Calculated Osmolarity: 785 mOsmol/liter
Concentration of Electrolytes (mEq/liter): Sodium 10; Chloride <3
Phosphate (HPO_4) 20 (10 mmole P/liter); Acetate Approx. 62 (provided as acetic acid and Iysine acetate)

CLINICAL PHARMACOLOGY

HepatAmine provides a mixture of essential and nonessential amino acids with high concentrations of the branched chain amino acids isoleucine, leucine, and valine, and low concentrations of methionine and the aromatic amino acids phenylalanine and tryptophan, relative to general purpose amino acid injections. This amino acid composition has been specifically formulated to provide a well tolerated nitrogen source for nutritional support and therapy of patients with liver disease who have hepatic encephalopathy.

The precise mechanisms which produce the therapeutic effects of HepatAmine are not known. The etiopathology of hepatic encephalopathy is also unknown and is thought to be of multifactorial origin. The rationale for HepatAmine is based on observations of plasma amino acid imbalances in patients with liver disease and on theories which postulate that these abnormal patterns are causally related to the development of hepatic encephalopathy.

Clinical studies in patients with hepatic encephalopathy showed that infusion of HepatAmine reversed the abnormal plasma amino acid pattern characterized by decreased levels of branched chain amino acids and elevated levels of aromatic amino acids and methionine. The trend toward normalization of these amino acids was generally associated with an improvement in mental status and EEG patterns. This clinical response was observed in the majority of patients studied. Nitrogen balance was significantly improved and mortality reduced in these typically protein-intolerant patients who received substantial amounts of protein equivalent as HepatAmine® (8% Amino Acid Injection).

When infused with hypertonic dextrose as a calorie source, supplemented with electrolytes, vitamins, and minerals, HepatAmine provides total parenteral nutrition in patients with liver disease, with the exception of essential fatty acids.

Phosphate is a major intracellular anion which participates in providing energy for metabolism of substrates and contributes to significant metabolic and enzymatic reactions in all organs and tissues. It exerts a modifying influence on calcium levels, a buffering effect on acid-base equilibrium, and has a primary role in the renal excretion of hydrogen ions.

It is thought that the acetate from lysine acetate and acetic acid, under the conditions of parenteral nutrition, does not impact net acid-base balance when renal and respiratory functions are normal. Clinical evidence seems to support this thinking; however, confirmatory experimental evidence is not available.
The amounts of sodium and chloride present are not of clinical significance.

INDICATIONS AND USAGE
HepatAmine is indicated for the treatment of hepatic encephalopathy in patients with cirrhosis or hepatitis. HepatAmine provides nutritional support for patients with these diseases of the liver who require parenteral nutrition and are intolerant of general purpose amino acid injections, which are contraindicated in patients with hepatic coma.

CONTRAINDICATIONS
HepatAmine is contraindicated in patients with anuria, inborn errors of amino acid metabolism, especially those involving branched chain amino acid metabolism such as Maple Syrup Urine Disease and Isovaleric Acidemia, or hypersensitivity to one or more amino acids present in the solution.

WARNINGS
This product contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.
WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.
Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.
Safe, effective use of parenteral nutrition requires a knowledge of nutrition as well as clinical expertise in recognition and treatment of the complications which can occur. **Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of parenteral nutrition.** Studies should include blood sugar, serum proteins, kidney and liver function tests, electrolytes, hemogram, carbon dioxide content, serum osmolarities, blood cultures, and blood ammonia levels.
Administration of amino acids in the presence of impaired renal function or gastrointestinal bleeding may augment an already elevated blood urea nitrogen. Patients with azotemia from any cause should not be infused with amino acids without regard to total nitrogen intake.
Administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, over-hydration, congested states, or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the solutions. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of the solutions.

PRECAUTIONS

General
Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require the use of additional electrolyte supplements.
Strongly hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.
Special care must be taken when giving hypertonic dextrose to a diabetic or prediabetic patient. To prevent severe hyperglycemia in such patients, insulin may be required.
Peripheral intravenous administration of HepatAmine® (8% Amino Acid Injection) requires appropriate dilution and provision of adequate calories. Care should be taken to assure proper placement of the needle within the lumen of the vein. The venipuncture site should be inspected frequently for signs of infiltration. If venous thrombosis or phlebitis occurs, discontinue infusions or change infusion site and initiate appropriate treatment.
Care should be taken to avoid circulatory overload, particularly in patients with cardiac insufficiency.
In patients with myocardial infarct, infusion of amino acids should always be accompanied by dextrose since in anoxia, free fatty acids cannot be utilized by the myocardium and energy must be produced anaerobically from glycogen or glucose.
Infusion of HepatAmine may not affect the clinical course of patients with fulminant hepatitis who have a poor prognosis and are generally unresponsive to treatment. It has been shown that the abnormal plasma amino acid pattern in fulminant hepatitis differs from that in chronic liver disease.
Extraordinary electrolyte losses such as may occur during protracted nasogastric suction, vomiting, diarrhea, or gastrointestinal fistula drainage may necessitate additional electrolyte supplementation.
Administration of glucose at a rate exceeding the patient's utilization rate may lead to hyperglycemia, coma, and death.

Metabolic acidosis can be prevented or readily controlled by adding a portion of the cations in the electrolyte mixture as acetate salts and in the case of hyperchloremic acidosis, by keeping the total chloride content of the infusate to a minimum.
HepatAmine contains less than 3 mEq chloride per liter.
HepatAmine contains 10 mmole/liter of phosphate. Some patients, especially those with hypophosphatemia, may require additional phosphate. To prevent hypocalcemia, calcium supplementation should always accompany phosphate administration. To assure adequate intake, serum levels should be monitored frequently.
HepatAmine has not been adequately studied in pregnant women and pediatric patients; therefore, its safe use in such patients has not been demonstrated.
To minimize the risk of possible incompatibilities arising from mixing this solution with other additives that may be prescribed, the final infusate should be inspected for cloudiness or precipitation immediately after mixing, prior to administration, and periodically during administration.
Use HepatAmine only if solution is clear, the seal unbroken, and vacuum is present.
Drug product contains no more than 25 μg/L of aluminum.

Laboratory Tests
Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring during administration.
Laboratory tests should include measurement of blood sugar, electrolyte, and serum protein concentrations; kidney and liver function tests; and evaluation of acid-base balance and fluid balance. Other laboratory tests may be suggested by the patient's condition.

Drug Interactions
Some additives may be incompatible. Consult with pharmacist. When introducing additives, use aseptic techniques. Mix thoroughly. Do not store.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No *in vitro* or *in vivo* carcinogenesis, mutagenesis, or fertility studies have been conducted with HepatAmine® (8% Amino Acid Injection).

Pregnancy

Teratogenic Effects - Pregnancy Category C.
Pregnancy Category C. Animal reproduction studies have not been conducted with HepatAmine (8% Amino Acid Injection). It is also not known whether HepatAmine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. HepatAmine should be given to a pregnant woman only if clearly needed.

Labor and Delivery
Information is unknown.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when HepatAmine is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of amino acid injections in pediatric patients have not been established by adequate and well-controlled studies. However, the use of amino acid injections in pediatric patients as an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance is well established in the medical literature.
See **WARNINGS** and **DOSAGE AND ADMINISTRATION**.

Geriatric Use
Clinical studies of HepatAmine did not include sufficient numbers of subjects age 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.
This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.
See **WARNINGS**.

Special Precautions for Central Venous Nutrition
Administration by central venous catheter should be used only by those familiar with this technique and its complications.

Central venous nutrition may be associated with complications which can be prevented or minimized by careful attention to all aspects of the procedure, including solution preparation, administration, and patient monitoring. It is essential that a carefully prepared protocol, based on current medical practices, be followed, preferably by an experienced team.
Although a detailed discussion of the complications is beyond the scope of this insert, the following summary lists those based on current literature.

Technical.
The placement of a central venous catheter should be regarded as a surgical procedure. One should be fully acquainted with various techniques of catheter insertion as well as recognition and treatment of complications. For details of techniques and placement sites, consult the medical literature. X-ray is the best means of verifying catheter placement. Complications known to occur from the placement of central venous catheters are pneumothorax, hemothorax, hydrothorax, artery puncture and transection, injury to the brachial plexus, malposition of the catheter, formation of arterio-venous fistula, phlebitis, thrombosis, pericardial tamponade, and air and catheter embolus.

Septic.
The constant risk of sepsis is present during total parenteral nutrition. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of solutions and the placement and care of catheters be accomplished under controlled aseptic conditions.

Solutions should ideally be prepared in the hospital pharmacy in a laminar flow hood. The key factor in their preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and subsequent admixtures.

Solutions should be used promptly after mixing. Any storage should be under refrigeration for as brief a time as possible. Administration time for a single bottle and set should never exceed 24 hours.

Consult the medical literature for a discussion of the management of sepsis. In brief, typical management includes replacing the solution being administered with a fresh container and set, and culturing the contents for bacterial or fungal contamination. If sepsis persists and another source of infection is not identified, the catheter is removed, the proximal tip cultured, and a new catheter reinserted when the fever has subsided. Non-specific, prophylactic antibiotic treatment is not recommended.

Clinical experience indicates that the catheter is likely to be the prime source of infection as opposed to aseptically prepared and properly stored solutions.

Metabolic.
The following metabolic complications have been reported during the use of central venous nutrition; metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, hypo- and hyper-vitaminosis, electrolyte imbalances and hyperammonemia in pediatric patients. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of therapy to prevent or minimize these complications.

ADVERSE REACTIONS
See **WARNINGS** and ***Special Precautions for Central Venous Nutrition***.
Reactions reported in clinical studies as a result of infusion of the parenteral fluid were water weight gain, edema, increase in BUN, and dilutional hyponatremia. Asterixis was reported to have worsened in one patient during infusion of HepatAmine® (8% Amino Acid Injection).
Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.
Symptoms may result from an excess or deficit of one or more of the ions present in the solution; therefore, frequent monitoring of electrolyte levels is essential.
Phosphorus deficiency may lead to impaired tissue oxygenation and acute hemolytic anemia. Relative to calcium, excessive phosphorus intake can precipitate hypocalcemia with cramps, tetany and muscular hyperexcitability.
If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

OVERDOSAGE
In the event of a fluid or solute overload during parenteral therapy, reevaluate the patient's condition, and institute appropriate corrective treatment.

DOSAGE AND ADMINISTRATION
The objective of nutritional management of patients with liver disease is the provision of sufficient amino acid and caloric support for protein synthesis without exacerbating hepatic encephalopathy.

The total daily dose of HepatAmine depends on daily protein requirements and on the patient's metabolic and clinical response. The determination of nitrogen balance and accurate daily body weights, corrected for fluid balance, are probably the best means of assessing individual protein requirements. Dosage should also be guided by the patient's fluid intake limits and glucose and nitrogen tolerances, as well as by metabolic and clinical response.

The recommended dosage is 80–120 grams of amino acids (12–18 grams of nitrogen) as HepatAmine® (8% Amino Acid Injection) per day. Typically, 500 mL of 8% HepatAmine appropriately mixed with 500 mL of 50% dextrose supplemented with electrolytes and vitamins is administered over an 8–12 hour period. This results in a total daily fluid intake of approximately 2–3 liters. Patients with fluid restrictions may only tolerate 1–2 liters. Although nitrogen requirements may be higher in severely hypercatabolic or depleted patients, provision of additional nitrogen may not be possible due to fluid intake limits, nitrogen, or glucose intolerance.

In many patients, provision of adequate calories in the form of hypertonic dextrose may require the administration of exogenous insulin to prevent hyperglycemia and glycosuria. To prevent rebound hypoglycemia, a solution containing 5% dextrose should be administered when hypertonic dextrose solutions are abruptly discontinued.

Fat emulsion coadministration should be considered when prolonged (more than 5 days) parenteral nutrition is required in order to prevent essential fatty acid deficiency (E.F.A.D.). Serum lipids should be monitored for evidence of E.F.A.D. in patients maintained on fat free TPN.

The provision of sufficient intracellular electrolytes, principally potassium, magnesium, and phosphate, is required for optimum utilization of amino acids. Approximately 60–180 mEq of potassium, 10–30 mEq of magnesium, and 10–40 mmole of phosphate per day appear necessary to achieve optimum metabolic response. In addition, sufficient quantities of the major extracellular electrolytes sodium, calcium, and chloride, must be given. In patients with hyperchloremic or other metabolic acidoses, sodium and potassium may be added as the acetate salts to provide bicarbonate precursor. The electrolyte content of HepatAmine must be considered when calculating daily electrolyte intake. Serum electrolytes, including magnesium and phosphorus, should be monitored frequently.

Pediatric Use

Use of HepatAmine in pediatric patients is governed by the same considerations that affect the use of any amino acid solution in pediatrics. The amount administered is dosed on the basis of grams of amino acids/kg of body weight/day. Two to three g/kg of body weight for infants with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance. Solutions administered by peripheral vein should not exceed twice normal serum osmolarity (718 mOsmol/L).

Hypertonic mixtures of amino acids and dextrose may be safely administered by continuous infusion through a central venous catheter with the tip located in the superior vena cava. Initial infusion rates should be slow, and gradually increased to the recommended 60–125 mL/hr. If administration rate should fall behind schedule, no attempt to "catch up" to planned intake should be made. In addition to meeting protein needs, the rate of administration, particularly during the first few days of therapy, is governed by the patient's glucose tolerance. Daily intake of amino acids and dextrose should be increased gradually to the maximum required dose as indicated by frequent determinations of glucose levels in blood and urine.

For patients in whom the central venous route is not indicated and who can consume adequate calories enterally, 8% HepatAmine may be administered by peripheral vein with or without parenteral carbohydrate calories. Such infusates can be prepared by dilution of 8% HepatAmine with Sterile Water for Injection or 5%–10% dextrose to prepare isotonic or slightly hypertonic solutions for peripheral infusion. It is essential that peripheral infusion be accompanied by adequate caloric supplementation. In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Care must be taken to avoid incompatible admixtures. Consult with pharmacist.

HOW SUPPLIED

HepatAmine® (8% Amino Acid Injection) is supplied sterile and nonpyrogenic in glass containers with solid stoppers packaged 6 per case.

NDC	Cat. No.	Size
HepatAmine® (8% Amino Acid Injection)		
0264-9371-55	S9371-SS	500 mL

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product. Protect from light until use.

Rx only

Revised: March 2007

Made in USA

Directions for Use of B. Braun Glass Containers with Solid Stoppers

Designed for use with a vented set.

Before use, perform the following checks:

1. Inspect each container. Read the label. Ensure solution is the one ordered and is within the expiration date.

2. Invert container and carefully inspect the solution in good light for cloudiness, haze, or particulate matter; check the bottle for cracks or other damage. In checking for cracks, do not be confused by normal surface marks and seams on the bottom and sides of the bottle. These are not flaws. Look for bright reflections that have depth and penetrate into the wall of the bottle. Reject any such bottle.

3. To remove the outer closure, lift the tear tab and pull up, over, and down until it is below the stopper (See Figure 1). Use a circular pulling motion on the tab until it breaks away.

4. Grasp and remove the metal disk, exercising caution not to touch the exposed sterile stopper surface.

Warning: Some additives may be incompatible. Consult with pharmacist. When introducing additives, use aseptic techniques. Mix thoroughly. Do not store.

5. Refer to Directions for Use of the set being used. Insert the set spike into the large round outlet port of the stopper and hang container.

6. After admixture and during administration, reinspect the solution frequently. If any evidence of solution contamination or instability is found or if the patient exhibits any signs of fever, chills or other reactions not readily explainable, discontinue administration immediately and notify the physician.

7. When adding medication to the container during administration, swab the triangular medication site, inject medication and mix thoroughly by gentle agitation.

8. Spiking, additions, or transfers should be made immediately after exposing the sterile stopper surface. Check for vacuum at first puncture of stopper. Admixture by needle or syringe should be made through the triangular (▽) medication site; contents should be drawn by vacuum into the bottle. Admixture by spiked vial should be through the outlet port (See Figure 2). If contents of initial addition are not drawn into the bottle, vacuum is not present and the unit should be discarded. Each addition/ transfer will reduce the vacuum remaining in the bottle.

9. If the first puncture of the stopper is the administration set spike, insert the spike fully into the outlet port of the stopper and promptly invert the bottle. Verify vacuum by observing rising air bubbles. Do not use the bottle if vacuum is not present.

10. If admixture or set insertion is not performed immediately following removal of protective metal disk, swab stopper surface.

B. Braun Medical Inc.
Irvine, CA USA 92614-5895

Y36-002-614

Revised: 11/2008

Distributed by: B. Braun Medical Inc.